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Existing data from our group suggest that Gulf War (GW) veterans score worse on a specific group of neuropsychological tests than GW-era veterans not deployed to the Gulf. These findings raise the possibility of subtle, "subclinical" central nervous system (CNS) damage associated with Gulf deployment. A critical question is whether these findings may be attributable to exposure to neurotoxicants in the Gulf environment.

Recently some PGW veterans have reported that their cognitive functioning has been worsening over the time since their return from the Gulf. This report is at odds with the usual course of CNS effects of intoxication, which generally remit or remain static in the absence of exposure. The reports of declining cognition raise the issue of exposure to toxicants that might produce a progressive condition versus the existence of other conditions that might affect cognition in individuals who are experiencing progressive functional declines.

The specific aims of the project are: 1) to determine whether objective test measures reveal progressive diminution in cognitive function by comparing test performance observed initially (1995-1998) to performance 4 years (+/- 6 months) later and 2) to identify the factors associated with any cognitive diminutions including chemical exposures, stress, or psychiatric disorders.

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FOREWORD

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INTRODUCTION

Our research completed to date indicates that Persian Gulf War (GW) veterans deployed to the Gulf score more poorly on a limited, specific group of neuropsychological test measures than GW-era veterans who were not deployed to the Gulf. These findings raise the possibility of subtle, "subclinical" central nervous system damage associated with Gulf deployment. The etiology of the neuropsychological deficits is unclear, but our data suggest that they are related to exposures experienced in the Gulf (Sullivan et al. submitted; White et al., 2001). Our data also suggest that these deficits cannot be attributed to stress, psychiatric status, or compensation seeking (White et al., 2001).

Recently some GW veterans who were deployed to the Gulf have reported clinically that their cognitive functioning has been worsening over the time since their return from the Gulf. Specifically, study participants report declines in the areas of short-term memory and concentration. Additionally, research subjects with high symptom complaints continue to report ongoing high symptom levels (SPProctor, personal communication). These reports are somewhat at odds with the usual course of central nervous system (CNS) effects of intoxication, which generally remit or remain static in the absence of exposure.

The specific aims of this project are: 1) to determine whether objective test measures reveal any progressive diminution in cognitive function by comparing test performance observed initially (1995-1998) to performance 4 – 5 years later among Gulf-deployed veterans compared to non-Gulf-deployed veteran controls, and 2) to determine whether any identifiable declines in function are related to Gulf-related environmental exposures, stress, psychiatric disorders, existence of multiple health complaints, normal aging, or motivational disorders.

Body

Background and Significance.

Environmental Exposures and Health Effects

The most commonly reported health related illnesses of Gulf War (GW) veterans included fatigue, headache, skin rash, joint or muscle pain, and loss of memory or other cognitive difficulties (Institute of Medicine report, 1996). The Department of Defense Comprehensive Clinical Examination Program (CCEP) data set further identified these symptoms as well as sleep disturbance, concentration problems, cough, and depression as commonly reported by a large study sample of 18,000 respondents (Roy, Chung 1994; Institute of Medicine report 1996). In studies conducted by Boston Environmental Research Hazards Center investigators, it has been found that veterans who were deployed to the Gulf reported their most prominent symptoms to be forgetfulness, fatigue, restless sleep, gastrointestinal disturbance, and pulmonary and cardiac symptoms (Proctor et al., 1998). In 1994, medical examinations of active duty GW veterans indicated that their most common diagnoses included diseases of the musculoskeletal system and connective tissue, mental disorders, ill-defined conditions, skin diseases, digestive system diseases, diseases of nervous system/sensory organs and infectious and parasitic diseases (CCEP, Joseph, 1997). A study of hospital discharges in 1992 and 1993 indicated no significant difference in overall risk for hospitalization in GW veterans compared with non-GW veterans. However, the specific diagnoses for which GW veterans were more frequently hospitalized included neoplasms, genitourinary diseases, blood diseases, and mental disorders (Gray et al., 1996). Longitudinal surveys of a large cohort of GW veterans have suggested that many veterans report their health symptoms to be gradually worsening since their original evaluations shortly after their return from the GW (SP Proctor, personal communication).

Persian Gulf War veterans may have been exposed to many environmental toxicants. Some researchers suggest that this may be the cause of their reported health complaints (US Senate Committee Rockefeller Report, 1995; Haley, 1997). These possible exposures include smoke from burning Persian Gulf oil wells (US Congress, Office of Technology Assessment, September, 1993), biological or

chemical nerve agents deployed by Iraq (Riegle, 1993), pre-deployment vaccines, anti-nerve gas agents (e.g., pyridostigmine), skin absorption of diesel fuel, airborne or material-based organic solvents, pesticides, parasitic infection (e.g., leishmaniasis tropica) and radiation from depleted uranium weaponry. Sarin a known neurotoxicant (Kadar et al., 1995), and mustard gas were reportedly detected in Saudi Arabia (Washington Post, Boston Globe, 11/1/93 and Boston Globe, 11/24/93). In addition, the US Department of Defense identified a chemical weapons arsenal at a destroyed storage site at Khamisiyah, Iraq. US military personnel charged with overseeing the destruction were unaware of the chemical weapons in this site and precautions were not taken against such exposures. In January 2001, the Pentagon revised its numbers of potentially exposed veterans by an additional 35,000 individuals. At other sites, measurements by US chemical warfare vehicles also reported unconfirmed measurement of the mustard gas lewisite as well as an unidentified blistering agent and benzyl bromide.

Sequelae from exposure to these environmental toxicants can include damage to multiple organ systems; for example, lewisite and mustard gases produce damage to the skin and respiratory system, and they appear to be potent carcinogens (e.g., Chevillard, Lainee, Robineau, & Puchelle, 1992; Pechura & Rall, 1993; Watson, Jones, & Griffin, 1989). Polycyclic aromatic hydrocarbons (PAHs) from oil smoke generate in vitro genotoxicity, adversely impacting immune and respiratory functions (e.g., Klaassen, Amdur, & Doull, 1986; Kelsey et al., 1994) and depleted uranium has been cited as having carcinogenic effects in addition to adverse effects on kidney functioning (Doucet, 1994). Other purported environmental exposures such as kerosene and diesel fuel (Andrews & Snyder, 1986); pyridostigmine (Almog et al., 1991; Keeler, Hurst, & Dunn, 1991; Van Haaren et al., 2001); metals and volatile organics found in smoke (Klaassen et al., 1986); and sarin (Burchfiel & Duffy, 1982; Kawabuchi, Cintra, Deshpande, & Dlbuquerque, 1991; Husain, Vijayaraghavan, Pant, Raza, & Pandey, 1993), exert both acute and chronic neurotoxicant effects in animals and humans. Although an incidence study of admissions to an Army hospital during the GW reported no admissions for exposure to chemical or biological weapons (Wintermeyer, 1994), it is possible that chronic low-level exposures may be the cause of cognitive and physiological changes as long-term sequelae are unknown in humans. In fact, a

recent report suggested that low-level neurotoxicant exposures may cause the delayed-onset neurotoxic syndrome OPIDP (organophosphate-induced delayed polyneuropathy) that may account for the varied symptoms of GW veterans (Kurt, 1998).

When evaluating effects of low level neurotoxicant exposures, neuropsychological evaluations are the instrument of choice because these tests can not only quantify behavioral deficits in persons with clinically obvious physical evidence of intoxication following exposure (Baker & White, 1985) as well as detect subtle dysfunction in exposed persons without obvious clinical disease. That is, even in the absence of overt toxicant poisoning, neurotoxicant exposed workers have been found to score significantly worse on specific neuropsychological tests than non-exposed workers. This condition has been referred to as "subclinical encephalopathy" (Baker, White & Murawski, 1985; White & Feldman, 1987; White et al., 2001).

Particularly important with regard to the possibility of identifying the specific relevant toxicants in a situation with multiple possible agents (such as in the GW) is the specificity of relations between particular toxicants and distinct neurobehavioral and neuropsychological effects (White et al., 1992). Epidemiological studies during the past 30 years have examined the impact of exposure to metals (e.g., lead, mercury, arsenic), organic solvents (e.g., trichloroethylene, n-hexane, petroleum distillates), and pesticides (e.g., organophosphates, carbamates) on cognitive functioning. For example, studies of solvent exposure have reliably shown disturbances in executive function, attention, visuospatial skills, short-term memory, and mood (e.g., Anger, 1990; Echeverria & White, 1992; White, Feldman & Proctor, 1992). Studies of lead-exposed workers have yielded similar findings along with decrements in verbal reasoning and motor functions (e.g., Baker et al., 1984; Hanninen, Hernberg, Mantere, Vesanto, & Jalkaner, 1978; Yokoyama, Araki, & Aono, 1988).

Neuropsychological functioning in Persian Gulf War Veterans

Recent neuropsychological evaluations of GW veterans have shown significant differences when compared to controls or when compared to published normative data (Goldstein 1996; Axelrod et al, 1997, Homm, 1997). These studies showed significant differences in GW veterans on measures of executive system functioning (Stroop test), two measures of motor functioning (Finger tap test, Purdue Pegboard test), and several overall impairment indexes including items from the Pittsburgh Occupational Exposure Battery and WAIS-R full scale IQ scores. It should be noted however, that some of these studies utilized small sample sizes (Goldstein, 1996, Hom et al., 1997) and did not include appropriate comparison groups (Axelrod, 1997). An additional study on one of these study groups (Axelrod et al., 1997) suggested that emotional functioning was correlated with observed cognitive deficits in GW veterans, such that impaired sustained attention was associated with trait anxiety, and depression was associated with poorer motor coordination and impaired executive system functioning (Sillanpaa et al. 1997). Hom et al, (1997) suggested from their findings that sick GW veterans showed generalized cognitive deficits rather than domain specific deficits. This pattern of cognitive deficit is not the usual course expected from mild neurotoxicant exposures (White & Proctor, 1997).

Existing data from our group (White et al., 2001) suggest that GW veterans score more poorly on a limited, specific group of neuropsychological test measures than GW-era veterans who were not deployed to the Gulf. These findings raise the possibility of subtle, "subclinical" central nervous system damage associated with Gulf deployment. A critical question about these findings is whether they may be attributable to exposure to neurotoxicants in the Gulf environment. This possibility is particularly salient because the existence of cognitive deficits was related in our sample to self-reported exposures to substances in the Gulf theater that are known to be neurotoxic.

Recently some GW veterans have reported that their cognitive functioning has been worsening over the time since their return from the Gulf. This report is at odds with the usual course of central nervous system (CNS) effects of intoxication, which generally remit or remain static in the absence of exposure. The reports of

declining cognition raise the issue of exposure to toxicants that might initiate a progressive condition versus the existence of other conditions that might affect cognition in individuals who are experiencing progressive functional declines.

Effects of Stress on Physical Health

The relationship between physical health symptoms and psychological stressors in GW veterans has raised several important questions regarding illness mechanisms. For instance, it has been found that stress and subsequent physiological arousal and anxiety is associated with subsequent reports of deteriorating health status, including cognitive declines in memory, concentration, and attention (e.g., Shalev, Bleich, & Ursano, 1990; Wolfe et al., 1992). Other investigators have suggested that prolonged stress can lead to long-term hormonal changes (Yehuda, 1997), reduced immune system functioning, (Black, 1994) and alterations of brain neurotransmitters that mediate cognitive and psychological responses (Wolfe & Charney, 1991). Studies based on animal models suggest that acute stress may also alter the permeability of the blood brain barrier to particular neurotoxicants (including pyridostigmine bromide; an acetylcholinesterase inhibitor given prophylactically to GW veterans as a protective measure in the event of chemical weapon attack (Friedman et al 1996; Van Haaren et al, 2001). However, other reports using rodent species could not replicate these findings (Lallement, 1998). Findings from our original evaluations of treatment-seeking GW veterans suggested that self-reported pyridostigmine bromide (PB) use was associated with lower scores on attention/executive system functioning (Wisconsin card sort test) and verbal memory functioning (California Verbal Learning Test) compared with veterans not reporting PB use. However, we were not able to confirm an interaction effect of reported PB use and severe stress reactions such as PTSD diagnosis (Sullivan et al., 2001).

To date, the symptoms reported by GW veterans have received no definitive diagnosis, and may not constitute a single diagnostic entity. A factor analysis by Haley et al. (1997) identified 6 possible syndrome types in this population that may represent delayed-onset neurotoxic syndrome variants.

These subtypes include impaired cognition, confusion-ataxia, arthro-myo-neuropathy, phobia-apraxia, fever-adenopathy and weakness-incontinence. Other investigators, after noting symptom complaints of fatigue, mood and musculoskeletal complaints in GW veterans, have suggested that half of these veterans would satisfy the criteria for chronic fatigue syndrome (Reeves, 1995). However, our original evaluation of 200 GW veterans found that <1 percent met clinical criteria for chronic fatigue syndrome. Other researchers suggest that infectious diseases are the cause of the varied symptoms noted by these veterans

(Nicolson et al, 1996; Oster et al., 1992; Kreutzer et al, 1993). Drug treatments are currently underway to assess if large doses of antibiotics may reduce complaints in veterans testing positive for mycoplasmic infections. Cross-sectional studies of veterans suffering from post-traumatic stress disorder (PTSD) have found that individuals with this diagnosis consistently report more physical health symptoms and poorer health status overall than their non-PTSD counterparts, (Kulka et al., 1990; Litz et al., 1992; Shalev et al., 1990; Kimerling & Calhoun, 1994; Wolfe et al., 1993). In addition, these veterans also showed lower salivary cortisol levels than their non-PTSD counterparts suggesting dysregulated immune system functioning (Kellner et al., 1999). However, we were unable to confirm any health complications from the synergistic effects of exposure to neurotoxicants combined with a stress induced reduction in immune functioning (Friedman et al, 1996) in our original evaluation of 200 GW veterans (Sullivan et al, submitted). In sum, there are several competing hypotheses for the varied symptoms reported by GW veterans. These etiologies include environmental exposures, post-traumatic stress disorder, chronic fatigue syndrome and multiple chemical sensitivity.

Post-traumatic Stress Disorder

The essential feature of PTSD is the development of characteristic symptoms following a psychologically traumatic event that is generally outside the range of usual human experience. The characteristic symptoms involve re-experiencing the traumatic event, numbing of responsiveness to or

reduced involvement with the external world, and a variety of autonomic, dysphoric, or cognitive symptoms (American Psychiatric Association, 1995).

Rates of presumptive PTSD in GW veterans vary considerably across samples (3-46%), dependent in part upon unit mission, unit composition, and location in the Middle East according to data from a longitudinal study of nearly 3,000 GW veterans (Wolfe et al., 1992; Wolfe et al., 1993). A recent meta-analysis by Haley (1997) suggested that incidence rates of PTSD in GW veterans were overestimated in some studies. Cognitive performance has been noted to be compromised in subjects with PTSD; problems with attention/mental tracking (e.g., span of apprehension) and executive system functioning (e.g., planning, anticipatory skills, monitoring) have been noted, but not problems with actual learning or memory (Sutker et al. 1995). Vasterling et al., (1998) noted difficulties with initial acquisition of information, retroactive interference, mental manipulation and sustained attention in GW veterans diagnosed with PTSD as well as apparent lower premorbid IQ. Depression (rather than PTSD) has been associated with attention and mental tracking problems. By comparison, elements of physical trauma in prisoners of war (e.g., percent captivity weight loss) have shown a significant association with learning and memory deficits. Overall, increased severity of PTSD, depression, and weight loss have been associated with greater rates of cognitive dysfunction (see also Levy, 1988). Our initial evaluations suggested no significant cognitive differences in performance of GW veterans with PTSD compared with GW veterans without a PTSD diagnosis. However, veterans with PTSD reported significantly more mood disturbances than their non-PTSD counterparts and suggest the need to control for mood disturbances when conducting cognitive evaluations of veterans with PTSD.

Multiple Chemical Sensitivity and Chronic Fatigue Syndrome

Many of the symptoms reported by GW veterans overlap with those associated with two other diagnoses whose etiology has not yet been determined: multiple chemical sensitivity (MCS) and chronic fatigue syndrome (CFS). A definition of MCS offered by Cullen (1987) has gained acceptance: symptoms triggered by an identifiable environmental exposure; present in more than one organ system; not explained on the basis of any standard test of organ system function; recurring and abating in response to exposure to chemicals of diverse structural classes that involve differing modes of action, at levels of exposure far below those typically known to produce adverse reactions in humans.

A definition of CFS offered by Fukuda et al. (1994) is frequently used: extreme fatigue lasting at least six months; producing a significant reduction in daily activities; not resolving with bed rest. The disorder may be accompanied by, but not predated by: self-reported short-term memory loss; sore throat; tender cervical or axillary lymph nodes; muscle pain; multi-joint pain without joint swelling/redness; headaches of a new type, pattern or severity; unrefreshing sleep; post-exertion malaise lasting more than 24 hours. The diagnosis using the 1994 criteria requires four or more of the above symptoms. These symptoms are commonly seen in GW veterans. Exclusionary criteria include: an active medical condition, such as untreated hypothyroidism; obesity; a previously diagnosed medical condition whose resolution has not been documented; past or current diagnosis of major depression, bipolar affective disorder, dementia, or schizophrenia; alcohol or substance abuse within 2 years. Results of our original study (1996-1998) suggested that although many GW veterans reported MCS and CFS like symptoms, very few met actual criteria for these diagnoses (<1 percent). Thus, it seems unlikely that GW syndrome can be attributed to either of these two diagnostic entities although all three illnesses may share some heretofore-unknown origin.

Overall Project Objective.

This study will focus primarily on longitudinal analyses and comparison of neuropsychological functioning among our previously examined GW-era treatment-seeking cohort. We will, however, also examine differences in health symptom report, and diagnostic outcomes (e.g., post-traumatic stress disorder [PTSD], and psychiatric disorders). Neuropsychological functioning was chosen as a primary focus because of its relevance to the multiple CNS complaints reported by GW veterans and because of the sensitivity of neuropsychological measures to the diagnoses of interest in this situation. We are specifically exploring potential associates of cognitive performance including (1) self-reported and available modeled dose estimates of environmental exposure, (2) pre-existing and current life stressors, and, (3) in the case of the deployed sample, Gulf experiences.

Preliminary or Pilot Studies.

1.Neuropsychological functioning in treatment-seeking GW-era veterans

The objective of this study was to compare the health status, environmental exposure history, and neuropsychological test results of treatment seeking GW-era veterans who were deployed to the Gulf (Research GW-deployed) and treatment seeking GW-era veterans who were not deployed to the Gulf (Research GW-non-deployed). Additional analyses were conducted using a clinically referred GW-deployed patient group as a comparison (Clinical-deployed). A sample of treatment seeking GW-era veterans who were seeking treatment or diagnostic evaluation for any type of health or adjustment complaint were the research subjects for this study. Subjects were chosen because they were listed as having been treated at any of the inpatient or outpatient treatment clinics at the Boston VA, the Manchester VA, the Lowell VA outpatient clinic or the Causeway Street Outpatient Clinic. A group of GW-deployed veterans who were referred specifically for neuropsychological evaluations because of increased health symptoms were also included. Subjects received the same protocol as described above. Comparisons of Gulf deployed and non-gulf deployed veterans were conducted. Analyses were completed controlling for age and education. Preliminary analyses of the neuropsychological data indicated that differences exist between treatment seeking GW-deployed veterans and treatment seeking non-deployed veterans when controlling for age and education. Differences exist in the domains of mood, short-term memory, and attention and executive system functions. Specifically, individuals who were deployed to the Gulf reported being more fatigued, had more difficulty acquiring and retaining verbal information, and made significantly more errors on tracking tasks (Sullivan et al., submitted). This study adds further support for the establishment of the feasibility and reliability of the methodology for the current study. This study also documents that there are differences in cognitive findings in individuals who were deployed to the Gulf versus their treatment-seeking veteran non-GW counterparts.

2. A Re-examination of Cognitive Functioning in GW-Era Veterans

A preliminary study of the re-examination of cognitive deficits in GW-era veterans included five veterans that had been tested twice by our clinic. A semi-structured questionnaire was administered and the veterans reported a significant decline in terms of health symptoms and cognitive function in the domains of short-term memory and mood. A preliminary analysis of change scores showed variability in performance from initial testing to follow-up. However, given the limited amount of data, analyses of predictor variables was not completed.

3. Comparison of Neuropsychological Function in Treatment-seeking and Non-Treatment Seeking GW Veterans

The objective of this study was to compare the health status, environmental exposure history, and neuropsychological test results of treatment seeking and non-treatment seeking GW veterans and to obtain preliminary data on the relation of neuropsychological functioning to the presence of health symptoms in the non-treatment seeking group.

A sample of treatment seeking GW veterans ($\underline{n} = 27$) received clinical neuropsychological evaluations after being referred to the neuropsychology service of the Boston DVAMC from clinical services such as neurology, psychiatry, vocational rehabilitation, and general medicine. The most common referral question was "rule out Gulf War Syndrome." The remaining referral questions were, "assess cognition," "rule out memory disorder," and "rule out disorders of attention and concentration." It is likely that all of these questions reflect similar concerns occasioned by patient complaints of CNS symptoms or the physician's impression that the patient might be experiencing the effects of CNS damage. As part of their neuropsychological evaluation patients received a semi-structured clinical interview, including questions concerning health symptoms.

A sample of non-treatment seeking GW veterans was obtained from among those recruited to date for an ongoing research study from among a cohort of approximately 3,000 military personnel deployed to the GW from Fort Devens, MA, and followed longitudinally since their return from the Gulf by Dr. Jessica Wolfe and Dr. Susan Proctor. The majority of the cohort had been administered a 20-item Health Symptom Checklist as part of an evaluation 18-24 months after their return. Analysis of these data indicated a median number of participants (51%) reported greater than 5 symptoms. This value was used to stratify the cohort into high symptom (5 or more symptoms) and low symptom (fewer than 5 symptoms) subgroups. A random sample of 24 high and 28 low symptom, non-treatment seeking, GW veterans was selected for comparison with the clinical group. This sample will be referred to here as the comparison research group.

All participants received an environmental interview, a clinical interview, psychological assessment measures and a brief neuropsychological test battery chosen from a more extensive battery that has been employed by Dr. White in prior work with subjects being assessed for toxicant-induced brain damage from environmental or occupational exposure (Binder, 1993). All of these tests have reliable psychometric properties and have been widely used for both research and clinical purposes. The tests are drawn from two major categories: (1) tests tapping relatively stable, premorbid cognitive/intellectual abilities and (2) tests shown to have high specificity and sensitivity for detecting changes in localized or diffuse cognitive brain functions (e.g., certain forms of attentional skill). Tests in the first category provide uniform estimates of baseline "premorbid" abilities for all individuals; the more specialized tests assess functions that may be differentially affected by a particular disease or condition such as those resulting from exposure to neurotoxicants (White et al., 1994).

The treatment seeking and both high and low symptom comparison research subgroups were comparable in age, education, and gender. On the majority of neuropsychological tests, differences between treatment seeking and both comparison groups were non-significant after adjustment of scores for differences in age, gender, and education. There were, however, several significant differences between treatment seeking veterans and comparison research subjects low in health symptoms. These differences were observed in tests

of complex attention (Trails B), motor speed (Finger Tapping with both dominant and non-dominant hands), and learning (California Verbal Learning Test). The treatment-seeking group also reported being more angry, confused, depressed, tense, and tired on the Profile of Mood States (POMS) than the low symptom comparison group. Comparisons between the treatment-seeking group and the high symptom research group yielded fewer differences. The treatment-seeking group made more errors on Trails B and tended to be slower with the dominant hand on a test of manual dexterity (Pegboard). In addition, the treatment-seeking group showed mild retrieval deficits on long-delay free recall on the CVLT compared to the high symptom comparison group. The treatment-seeking group reported being more angry, confused, depressed, tense, and tired on the POMS than the non-treatment seeking high symptom group.

These data suggest that treatment-seeking GW veterans demonstrate a restricted set of impairments in cognitive abilities compared to non-treatment seeking GW veterans with few health complaints. Differences in neuropsychological functioning between treatment-seeing GW veterans and those non-treatment seeking veterans who reported relatively more health complaints were fewer in number. These findings suggest a relation between neuropsychological deficits and the presence of health symptoms in veterans of the GW. The small number of neuropsychological differences that were observed when treatment-seekers were compared with non-treatment seekers with relatively high numbers of health symptoms may relate to differences in the number or type of symptoms in these groups, or may reflect other differences between treatment-seekers and non-treatment-seekers.

4. Diagnostic Outcomes in Non-Treatment-Seeking GW Veterans as Compared With a Non-Gulf Deployed Control Group

The objectives of this study conducted by White and colleagues (2001) were to determine the type and frequency of health symptoms in non-treatment seeking GW veterans, to determine the frequency with which

this group met criteria for several neurobehavioral diagnoses, to evaluate their neuropsychological functioning, and to obtain data on their environmental exposure history to relate to these findings.

The study population was selected from a larger cohort of GW veterans according to an a priori sampling scheme. Sampling was devised to equally represent high and low symptom groups from the Ft. Devens cohort of GW-deployed veterans (as previously described) and the group was oversampled for women. Preliminary analyses of 220 GW deployed and 50 Germany deployed veterans are reviewed below.

Subjects received the same protocol as described in the first study. Subjects included random samples of earlier survey responders from the Devens cohort and a group of Germany deployed veterans (National Guard medical unit from Bangor, ME, deployed to Germany at the time of the GW). Comparisons of Gulf and Germany deployed groups, adjusted for sampling design, age, education, and gender were made using SUDAAN. Additionally, comparisons were done of Gulf and Germany deployed groups, controlling for covariate effects such as age, education, gender, race, pre-existing medical concerns, occupational exposures, PTSD or other psychiatric diagnoses, and deployment status.

Preliminary analyses indicated the following health symptoms, in order of frequency: aches and pains, skin rash, fatigue, headache, intestinal problems, and difficulties with memory and concentration. Affective disorders were diagnosed as follows: 7.3% met criteria for current Major Depressive Disorder; 21.6% for lifetime Depressive Disorder, approximately 5% for current PTSD, and 8% for lifetime PTSD.

Analyses of the neuropsychological data indicated differences between GW deployed veterans and Germany deployed veterans in the areas of motor functioning, mood, and learning. Specifically, differences existed after controlling for covariates including PTSD and Major Depression on measures of simple tracking, memory, and mood. Subtle differences were also found on measures of mood and attention between those Gulf-deployed subjects reporting pesticide exposure and those reporting no exposure, after controlling for covariates, including PTSD and Major Depression.

These studies established the feasibility and reliability of the methodology for the present study. It was found that differences exist in the areas of motor functioning, mood, and learning between Gulf-deployed and

non-deployed veterans in a cross-sectional study. In addition, the veterans with neurotoxicant exposures differ from veterans with no exposures on measures of mood and attention.

RESEARCH DESIGN AND METHODOLOGY

A. Purpose

The preliminary studies described above indicate that there is a relationship between the health status of GW veterans and neuropsychological functioning and that these deficits persist over time. What is not known is whether these deficits are progressive. While CNS symptoms are common among GW veterans' health complaints, the contribution of service in the GW to CNS symptomatology has remained unclear. The evaluation of CNS dysfunction over time, and, more specifically, the etiology of any progressive cognitive deficits that can be identified, is the primary focus of the present study. The secondary purpose is to relate the patterns of chronic neuropsychological impairments seen to other variables. We are also interested in understanding the prolonged impact of several variables, including environmental exposures, pre-existing and post-deployment life stressors, psychiatric disorders, existence of multiple health complaints and motivational factors on the study outcomes.

The four preliminary studies described above have indicated that there is a relationship between the health status of GW veterans and neuropsychological functioning: veterans with greater numbers of health symptoms showed a greater number of neuropsychological impairments than did those with fewer symptoms. This suggests that there may be a CNS component to their health complaints. However, the findings leave open the nature of the contribution of service in the GW to these findings. The evaluation of this contribution is the primary purpose of the proposed study. The secondary purpose is to relate the observed patterns of neuropsychological impairments to other variables. The specific aim is to determine whether there are differences in cognitive performance, current health symptom reports, and diagnostic outcomes among the groups of GW deployed and non-deployed treatment-seeking GW-era

veterans. We are also interested in understanding the impact of several variables, including environmental exposures, pre-existing and post-deployment life stressors, and Gulf experiences on the study outcomes.

B. Study Design

1. Overview

GW-era veterans who were tested previously in our laboratory are the participants in this study. A group of patients who were initially referred for clinical neuropsychological evaluations (clinical sample) have been re-examined. In addition, a group of individuals who were seeking treatment or diagnostic evaluation for any purpose and who were tested previously (DoD DAMD 17-96-1-6043) are also included in the study sample. As in our pilot studies, test scores from individuals who were deployed to the Gulf are compared with test scores from those who were not deployed. Additionally, longitudinal analyses will be conducted in order to examine changes in test performance over time. The assessment instruments employed in the study of treatment-seekers are basically the same as those utilized in the preliminary studies described above.

Study Sample

One hundred and fifty subjects will be examined in three years. Subjects are recruited on the basis of the original test date and are tested approximately 4 years (+/- 6 months) after the last neuropsychological evaluation. The recruitment procedure is outlined below. To be consistent with the original recruitment pattern, 75 participants would need to be recruited in the year 1 of the study followed by 50 participants in year 2 and 25 participants in year 3.

Initial Contact. The first contact with potential participants occurs by telephone (or by mail, if there is no telephone number available). The initial contact consists of a description of the follow-up study, reminding subjects of the types of assessment, time required, and reimbursement for their time and effort.

Subjects have an opportunity to ask questions about the procedures. They are also reminded to not inform the examiners of their Gulf deployment status until the conclusion of the neuropsychological evaluation. They are informed that whether or not they participate will have no bearing on their medical care and that, if they choose to participate, they may withdraw at any time without prejudice. Potential participants are asked to indicate whether they wish to participate, wish not to participate, or wish to defer this decision. In the latter case they are asked whether we may contact them again to determine their decision. Those consenting to participate are asked questions to determine whether they meet preliminary inclusion criteria for the study (that is, that they are not currently in treatment for alcohol or other substance abuse, do not have sensory or motor impairments precluding use of the computer, and did not sustain serious brain injury since the last test session). Prior substance abuse and current medications are recorded but do not constitute exclusion criteria. An appointment at the Boston DVAMC or during one of the field trips is scheduled for patients agreeing to participate. Veterans retained in the study sample are presented the study consent form for signature.

3. Assessment Instruments and Procedures

a. Behavioral Inventories

1. Cognitive Assessment.

A tester who is blind to the deployment status of the subject administers the neuropsychological test battery. The neuropsychological test battery assesses the functional domains of general intelligence, attention, executive abilities, motor function, visuospatial skills, memory, and mood. The battery is described in detail in Table 1. It includes 1) tests designed to tap relatively stable native intellectual abilities (e.g.,WAIS-R Information subtest), and 2) tests shown to have high specificity and sensitivity for detecting changes in neuropsychological functions attributable to neurotoxicant exposures and psychiatric disorders (White et al., 1992).

Because it is anticipated that issues related to compensation for disability may be pertinent for many of these veterans who may also be treatment seeking and compensation seeking, the possibility of motivational factors affecting test performance (Binder, 1992; Binder, 1993) are addressed directly. This is accomplished in two ways: 1) by inclusion of internal consistency checks in certain neuropsychological test measures (e.g., test/item repetition, easy/hard item comparisons) and evaluation of response style (over-endorsement, response approximations) and 2) by administering the Test of Memory and Malingering (TOMM; Tombaugh, 1996).

Table 2. Full Neuropsychological Test Battery; Tests in Preliminary Studies Marked *

I. Tests of General Intelligence

Test Name	Description
1. Wechsler Adult Intelligence Scale-Revised (WAIS-R)(53)	Information usually learned in school; to assess native intellectual abilities
Information subtest	

II. Tests of Attention, Vigilance, and Tracking

Test Name	Description
1. Digit Span Subtests: WAIS-R*	Oral recall of digits forward and backward; Given twice to assess
Wechsler Memory-Scale-Revised (WMS-R)	consistency of performance
2. Trail making Test*	Timed connect-a-dot task to assess attention and motor control requiring sequencing (A) and alternating sequences (B)
2. Continuous Performance Test (CPT)* (NES)	Target letter embedded in series of distracters; to assess sustained attention and reaction time
4. Paced Auditory Serial Addition Test * (PASAT;)	Continuous addition test; to assess sustained attention under distracting conditions
5. Wisconsin Card Sorting Test* (WCST)	Requires use of feedback to infer decision making rules; assesses problem solving ability and flexibility (64 cards only)

III. Tests of Motor Function

Test Name	Description
1. Finger Tapping*	Speed of tapping with index finger of each hand assesses simple motor speed

2. Purdue Pegboard Test*	Speed of inserting pegs into slots using each hand separately and both together

IV. Tests of Visuospatial Function

Test name	**Description**
1. WAIS-R Block Design*	Using blocks to replicate 2-dimensional designs; to assess visuoconstruction
2. Hooper Visual Organization Test * (HVOT)	Identifying objects from line drawings of disassembled parts; assesses ability Synthesize visual stimuli

V. Tests of Memory

Test Name	**Description**
1. Paired Associate Learning-WMS-R*	Recall of second member of pairs of words immediately and after a delay; assesses short-term memory and recall
2. Visual Reproductions-WMS*	Reproductions of visual designs, immediately and after a delay; assesses short term memory and recall
3. California Verbal Learning Test* (CVLT)	List of 16 nouns from 4 categories presented over multiple learning trials with recall after interference

VI. Tests of Personality and Mood

Test Name	**Description**
1. Profile of Mood States* (POMS)	65 single word descriptors of affective symptoms are endorsed for degree of severity and summed on six mood scales

VII Tests of Malingering

Test Name	**Description**
1. Test of Memory and Malingering* (TOMM)	Immediate forced choice recognition of line drawings of 50 common objects; assesses motivation and malingering

2. **Psychological Assessment.**

1) Participants are administered the Structured Clinical Interview for DSM-III-R (SCID, Spitzer et al, 1990) and a current Global Assessment of Functioning. The SCID has demonstrated reliable psychometric properties for determining the presence or absence of current or past major Axis I psychiatric disorders. Dr. Krengel will re-administer the Clinician Administered PTSD Scale (CAPS; Blake, 1990a), a state-of-the-art instrument for confirming the diagnosis of current or past PTSD and for evaluating the intensity, frequency, and severity of the disorder and its individual symptom criteria. Extensive research now indicates that this instrument has highly acceptable psychometric properties (Weathers et al., submitted). Study participants fill out a series of self-report, paper-and-pencil measures designed to confirm and define symptoms of PTSD (Mississippi Scale for PTSD; Keane 1988), to describe war-zone exposure (modified Laufer Combat Exposure Scale; Gallops, 1981), and to identify traumatic events occurring since last assessment.

2) Dr. Krengel also conducts a semi-structured clinical interview eliciting information pertaining to recent past and current mood disorders, substance use, neurological and medical illness, traumatic brain injury, and history of other traumatic events. Study participants are also asked questions specifically related to recent occupational history (including possible occupational exposure to neurotoxicants), family history of psychiatric disorder, and life stressors since the time of the last evaluation. Any treatment programs initiated since the last assessment are documented.

3) Study participants complete a symptom checklist consisting of a comprehensive list of frequently reported health and mental health symptoms, which is compared to their previous questionnaire data.

b. Environmental Exposure Assessment

For the purpose of this study, the environmental interview used in previous studies (Wolfe et al., 1998) has been modified as a questionnaire. The questionnaire includes items pertaining to recent occupational and environmental exposures. The original semi-structured interview schedule includes details related to GW

service including past military and health experiences, pre-military environmental exposure and health. Included is length of stay, geographical location, unit/individual duties, movement in the theatre, and environmental exposure during deployment (type, intensity, frequency, duration, locale). The environmental health specialist (Dr. Susan Proctor) is available to interview subjects in the event that questionnaire data concerning environmental and occupational exposures need clarification or when a more extensive interview is required.

This study also makes use of objective data on geographical locations and cumulative exposure at the unit level for the clinical subjects (obtained from D. Hakenson, Center for Research on Unit Records, [RUR], U.S. Army, personal communication). RUR is directly involved with the determination and computerization of all U.S. military locations during the war, including grid coordinates and longitude/latitude demarcations. This information is linked with existing environmental data (e.g., concentrations of oil smoke particulates modeled by the U.S. Army Center for Health Promotion and Preventative Medicine (CHPPM)). With input from this team, we will seek information on objective exposure measures and will integrate these data with the geographical locations reported by our study participants to better estimate individual cumulative exposure for the sample of participants deployed to the Gulf.

Data Analysis

Treatment of Data

Preliminary analyses will be conducted to check for baseline differences in those who have agreed to participate and those lost to follow-up. A comparison of treatment seekers versus non treatment-seekers on education, combat exposure, and other characteristics of interest will be completed. In addition, we will explore the relationship of symptom reporting and diagnostic outcome between the groups and its correlation with change in neuropsychological test performance.

The aims of this study are to determine whether there has been a diminution in performance on neuropsychological tests from the initial testing to follow-up in the GW sample and to explore subject characteristics and individual risk factors in Gulf exposure in accounting for this change.

a. Analyses will focus on **difference** scores describing change in performance in follow-up and initial test performances. A crude comparison between the average change in performance for the Gulf-deployed versus non-deployed group will be conducted through a paired sample t-test. A comparison of GW-deployed and non-deployed groups on average change in performance adjusting for intervening factors will be conducted through analysis of covariance.

b. In addition, we will split the GW sample into treatment seekers and the clinical sample and make a comparison across the 3 groups using a 1-factor analysis of variance on the average difference scores. We will examine baseline characteristics that might be related to change in neuropsychological performance and examine change in intervening events or stressors that might relate to change in performance.

For another aim of this study, focusing on the role of neurotoxicant exposure in the Gulf, we will examine the relationship between experience in the Gulf and change in neuropsychological performance through multiple regression. These analyses will include indicator variables to account for group status (1= Gulf deployed clinical sample, 2= Gulf deployed treatment seekers, 3= non-deployed) as well as individual risk factors and intervening risk factors that might be related to outcomes. Additional analyses exploring interactions between exposures and change in performance will be pursued. We will look at the relationship of stress, psychiatric diagnoses and disability status, and normal aging through multiple regression analyses as described above.

KEY RESEARCH ACCOMPLISHMENTS

STATUS/RESULTS TO DATE

The objective of this study is to determine whether veterans of the Gulf War (GW) show cognitive impairments suggestive of central nervous system damage at a greater rate than do GW-era veterans who were not deployed to the Gulf. A further study objective is to assess whether the GW veterans' symptoms are becoming worse since their first evaluation approximately four years ago. The diagnostic protocol for these evaluations includes an environmental exposure questionnaire, a psychological assessment and a neuropsychological evaluation. The environmental questionnaire is overseen by an environmental health specialist (Dr. Proctor) and assesses health experiences, geographical location, unit/individual duties, and environmental exposures during deployment to the Gulf (type, intensity, frequency, duration, locale), and/or during military service in general. In addition, subjects are queried about current health symptomatology including evaluation of chronic fatigue syndrome and multiple chemical sensitivities. The psychological assessment is administered by a clinical psychologist (Dr. Krengel) and includes the administration of the Structured Clinical Interview for DSM-IV (SCID; Spitzer et al., 1990), the Clinician Administered PTSD scale (CAPS-DX; Blake et al, 1995) and a semi-structured clinical interview. The SCID interview is reliably used to determine Axis I disorders (Wolfe & Keane, 1993) and the CAPS-DX is a state of the art instrument for confirming the diagnosis of current and/or lifetime PTSD, as well as, for evaluating the intensity, frequency and severity of the disorder and its individual symptom criteria. The semi-structured clinical interview administered by Dr. Krengel elicits information pertaining to current or past mood disorders, substance abuse, neurological and medical illness, traumatic brain injury, history of other traumatic events, birth trauma, developmental delays, and history of learning disability. This interview includes a follow-up of any medical or social changes since the study participant's last evaluation. Subjects are asked questions specifically related to changes in school achievement, and occupational history (including possible occupational exposure to neurotoxicants), family history of psychiatric disorder, and post-deployment

stressors. The neuropsychological test battery is administered by trained professionals. The total time to complete the study protocol is approximately 3-4 hours.

This longitudinal study is still in the data collection phase and our enrollment at this time includes 91 study participants from the original randomized list of GW-era veterans (15 women, 76 men). Of this group, 78 subjects are GW veterans and 13 subjects are non-GW veterans. Specifically, of the 78 GW veterans recruited, 23 were treatment-seekers and 55 were from the clinical sample. Our initial projection for year 2 recruitment was 125 study participants. Although our total recruitment numbers remain below our initial projections, the ratio of clinical, treatment-seeking and non-GW veterans was within expectation given our original recruitment ratios. The majority of control veterans were not recruited in the first years of the original study and therefore, have not met the predetermined time period (4 years) between evaluations. Therefore, the focus for year 3 will include emphasis on non-GW and treatment-seeking veteran recruitment and less emphasis on clinical GW veteran recruitment. In terms of total study recruitment, a slow start-up phase and minor nonlocation difficulties in Year 1 brought our recruitment total below our initial projections (44/75 participants). Although we improved our recruitment during the past year, our total recruitment for year 2 still remained below our initial projections (91/125 participants). However, we have employed several new strategies to improve our recruitment efforts including traveling to other VA medical centers closer to our participants homes. These recruitment trips have greatly increased our recruitment efforts. In fact, a recruitment trip is currently planned for March 1st to recruit an additional 10 study participants from the New Hampshire area. In addition, we also included weekend appointments for participants unable to come for appointments during the week. We have also continued to update residence locations through a federal interagency agreement, performed national yellow page searches on the internet and contacted reported next of kin. These strategies have improved our study participant contact ratio and will allow us to improve our recruitment efforts in order to meet our goal of 150 study participants in year 3 of the project.

In terms of reportable outcomes, preliminary results were presented in the form of two posters at the American Psychological Association annual meeting in San Francisco, CA in August, 2001. The preliminary data analyses were based on scores from our first 48 study participants. The analyses involved paired sample t-tests comparing participants' performances at Time 1 and Time 2 evaluations. These preliminary analyses suggested relatively that test-retest performances in GW veterans were relatively static over the four-year time interval. These preliminary findings did not support continued diminution of veteran's performances on neuropsychological measures. However, these performances also did not suggest improvement of cognitive functioning over this time period. Preliminary analyses of mood changes in the first 48 study participants were also conducted using paired sample t-tests and suggested that mood-state at the time of the testing has changed during the past four years. Specifically, veterans reported lower levels of tension, anger and confusion after four years. However, the GW veterans reported equivalent levels of fatigue when compared with their original assessments.

FUTURE DIRECTIONS

This sample was also examined using the same measures as a sample already studied by the investigators (BEHC Ft. Devens sample, n = 220), who were seen as part of a cohort study of deployed GW veterans. Using data from these two samples, it is now possible to examine separately the effects of treatment seeking, deployment, diagnosis, and GW exposures on various outcome measures.

When comparing the original testing of the GW-deployed treatment seeking sample (DoD) to the largely non-treatment seeking sample (BEHC), it was found that treatment seeking veterans performed worse on a significant number of cognitive tasks (in the functional domains of attention, executive skills, fine manual motor dexterity, visual constructive ability, and short-term memory). They also reported greater dysphoria on mood scales. The current study will help determine whether these patterns persist in the treatment-seeking cohort four-years after their first evaluations. In addition, a grant proposal for a re-evaluation of the BEHC Fort Devens sample is currently under review (VA CSP # 527). If funded, it will

then be possible to compare test-retest measures for both study cohorts. This will allow for a more complete picture of GW veterans cognitive functioning.

In our original evaluations of treatment seekers, deployment status (deployed versus non-deployed) had no effect on likelihood of being diagnosed with PTSD (13.2% deployed, 10.8% non-deployed), or MCS or CFS (<1% in all groups). The current follow-up study will continue to assess for these syndromes and will document any changes in diagnostic incidence.

In our original evaluations, PTSD diagnoses and deployment status were associated with poorer performance on neuropsychological tests in three domains (attention, visual construction, memory) and with greater mood complaints, though the findings were less pronounced than those seen when comparing treatment seekers to non-treatment seekers. These findings raise the possibility that treatment seekers are experiencing CNS dysfunction from some cause that is not unknown. PTSD is one candidate, but this diagnosis does not explain all of the findings. In the DoD (treatment-seeking) deployed sample, self-reported exposure to pesticides, burning human waste with diesel fuel and PB were considered as explanations of CNS dysfunction, but exposure-outcome relationships were not confirmed. We will continue to assess for these relationships in the current follow-up examination. However, due to the small incidence of these diagnoses and potential for Type II error, it seems appropriate to perform these analyses when more study participants have been recruited.

Reportable outcomes

Abstracts have been accepted for presentations at scientific meetings. In addition, two manuscript has been accepted for publication and an additional manuscript has been submitted for publication.

Abstracts:

1. Neuropsychological findings among Persian Gulf War-era veterans, presented at International Neuropsychological Society meeting in Honolulu, Hawaii, February 1998.

2. Relationship of PTSD and depression to Persian Gulf health problems, presented at the Conference on Federally Sponsored Gulf War Veterans Illnesses research meeting in Washington, D.C., June 1998.

3. Neuropsychological Findings Among Persian Gulf War-era veterans, presented at the Conference on Federally Sponsored Gulf War Veterans Illnesses research meeting in Washington, D.C., June 1998.

4. Neuropsychological test methods in assessment of neurotoxicant exposure in Persian Gulf War-era veterans, presented at the Theoretical and Experimental Neuropsychology annual meeting, June 1998.

5. Neuropsychological deficits in treatment-seeking Persian Gulf War-era veterans, presented at the Conference on Federally Sponsored Gulf War Veterans' Illness Research, June, 1999.

6. Neuropsychological deficits in treatment-seeking Persian Gulf War-era veterans, presented at the International Neuropsychological Society annual meeting in Denver, Colorado, February, 2000.

7. Neuropsychological deficits in association with stress reaction and pyridostigmine bromide intake in Persian Gulf War-era veterans, presented at the International Neuropsychological Society annual meeting in Denver, Colorado, February, 2000.

8. Neuropsychological deficits in association with stress reaction and pyridostigmine bromide intake in Persian Gulf War-era veterans, presented at the Conference on Federally Sponsored Gulf War Veteran's Illness Research, January 2001.

9. A re-examination of neuropsychological functioning in Gulf War-era veterans, submitted for presentation to the American Psychological Association annual meeting in San Francisco, CA, August, 2001.

10. A re-assessment of current mood state in Persian Gulf War-era veterans, submitted for presentation to the American Psychological Association annual meeting in San Francisco, CA, August, 2001.

Published Manuscripts:

White et al., (2001). " Neuropsychological function in Gulf War Veterans: Relationships to self-reported toxicant exposures." American Journal of Industrial Medicine, 40, 42-54.

Proctor, S.P. (2000). Chemical Sensitivity and Gulf War Veterans Illnesses. Occupational Medicine: State of the Art Reviews, 15 (3), 587-599.

Sullivan et al., manuscript submitted entitled " Neuropsychological deficits in association with stress reaction and pyridostigmine bromide intake in GW-era veterans."

Planned manuscripts: Proctor et al., manuscript planned entitled "Comparison of functional status (as measured by SF36) in clinical and research studies of GW-deployed military personnel."

Proctor et al., manuscript planned entitled "Methodology to assess environmental exposures in GW-deployed military personnel."

Krengel et al., manuscript planned entitled " Neuropsychological functioning in GW-era veterans."

Conclusions:

The preliminary analyses of the test-retest measures for the first 48 study participants suggest relatively static cognitive performances and slightly less robust mood complaints in GW veterans within a four-year time interval. These preliminary findings do not support continued diminution of veteran's performances on neuropsychological measures. However, neither do these performances suggest improvement of cognitive functioning over this time period. It is possible that this relatively static performance in our GW veterans could be consistent with long-term patterns expected from neurotoxicant exposure. However, continued follow-up of cognition and mood and a full study sample should provide a clearer picture of this pattern.

The study has the following clinical implications:

1). CNS complaints of GW-era veterans should be taken seriously and explored with formal testing and neuropsychological diagnosis.

2). Mood complaints are common among deployed and non-deployed GW-era veterans.

3). PTSD occurs in GW-era veterans (10-13%) and may be related or unrelated to the war. Possibility of its existence should be considered.

4). GW exposure to environmental agents should be considered in evaluation of GW veterans' health.

5). Evaluation of CFS and MCS should be done carefully, with established diagnostic criteria. CFS- and MCS-like symptoms are probably more common than the full blown syndromes.

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A Re-examination of Neuropsychological Functioning in Gulf War-Era Veterans

Introduction:

Existing data from the Boston Environmental Hazard's Research Center suggest that Persian Gulf War (PGW) era veterans deployed to the Gulf have deficits on a limited, specific group of neuropsychological test measures as compared to PGW-era veterans who were not deployed to the Gulf. These findings raise the possibility of subtle, subclinical central nervous system damage associated with Gulf deployment and raise the question of whether such changes may be attributable to exposure to neurotoxicants in the Gulf environment. This latter possibility is particularly an issue because the existence of relative cognitive deficits was related in our sample to self-reported environmental exposures that are likely neurotoxic.

Recently some PGW veterans have reported that their cognitive functioning and mood complaints are worsening over the time since their return from the Gulf. Veterans are specifically reporting further deficits in the areas of short-term memory and attention. For instance, veterans report that they are having more difficulty remembering names and appointments and they are having difficulty completing work-related tasks. These reports are at odds with the usual course of central nervous system (CNS) effects of intoxication, which generally remit or remain static in the absence of exposure.

The specific aim of the project was to determine whether objective neuropsychological test measures reveal any progressive diminution in cognitive function among Gulf deployed PGW veterans by comparing test performance observed initially (1995-1998) with performance 4 years (+/- 6 months) later.

Subjects:

In our initial study, 207 PGW-deployed treatment seeking veterans were administered a thorough neuropsychological test battery including assessment measures from the domains of memory, attention and executive systems, visuospatial, language, motor and mood. Overall, neuropsychological deficits were found in the areas of attention and short-term memory when controlling for age, education and mood. Twenty-four individuals from our original GW deployed sample have been tested for a second time approximately four years after their first evaluation.

Preliminary Results:

Results of paired T-tests indicated similar performances on tests from most domains including attention and executive functions. The only significant finding was in the domain of nonverbal memory, specifically the WMS-R visual reproductions delayed recall. This performance improved significantly relative to the first testing.

Summary:

These preliminary results from our first 24 subjects suggest relatively static performances in GW veterans on test-retest measures with a four-year interval. These preliminary findings do not support continued diminution of veteran's performances on neuropsychological measures. However, neither do these performances suggest improvement of cognitive functioning over this time period. These results will be discussed as they relate to etiologic factors including possible neurotoxicant exposures. It is possible that this relatively static performance in our GW veterans could be consistent with long-term patterns expected from neurotoxicant exposure. However, continued follow-up of cognition and mood in these veterans should provide a clearer picture of this pattern.

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A Re-assessment of current mood state in Persian Gulf War-Era Veterans

Introduction:

It has been found that Persian Gulf War (PGW) deployed veterans have reported a variety of mood complaints including depression, tension, anger and confusion since their return from the Gulf. These mood complaints have been reported to effect performance at work and have impacted social functioning, according to many PGW-deployed veterans. Some researchers have also found that these mood symptoms have had an effect on performance on a limited number of neuropsychological tests. Existing data from the Boston Environmental Hazard's Research Center suggests that PGW veterans deployed to the Gulf have significantly more mood complaints than their non-deployed counterparts. Although these complaints coexist with impairments in specific cognitive domains, we have found that neuropsychological deficits persist when controlling for current mood state. Given the impact of current mood on daily functioning, it is important to monitor mood state in PGW-deployed veterans in order to assist individuals in developing strategies to enhance social and occupational functioning.

We are currently following a clinical sample of over 200 PGW-era veterans, over half of whom were deployed to the Gulf during the war. Clinically, many of the PGW- era deployed veterans continue to report mood changes that have reportedly magnified over time since their return from the Gulf. Specifically, PGW-era deployed veterans report increased amounts of tension, depression and fatigue during clinical interview at a significantly higher rate than their non-deployed peers.

The specific aim of the current project was to determine whether mood measures revealed any progression of mood complaints among Gulf deployed PGW veterans by comparing scores observed initially (1995-1998) and those 4 years (+/- 6 months) later.

Subjects:

In our initial study, 207 PGW-deployed treatment seeking veterans were administered a thorough neuropsychological test battery including assessment measures from the domains of memory, attention and executive systems, visuospatial skills, language, motor speed and dexterity, and mood. PGW-era deployed veterans complained of fatigue, tension, depression, anger and confusion when compared to PGW-era nondeployed veterans. Twenty-four individuals from our original PGW-era deployed sample have returned to our clinic for follow-up. These individuals were interviewed and assessed for a second time approximately four years after their first evaluation.

Preliminary Results:

Results of paired T-tests indicated equal results for fatigue over four years in the deployed group, whereas levels of tension and anger diminished slightly relative to initial assessment. Confusion declined significantly from prior reports ($p = .05$). The only clinically significant mood complaint in this group of individuals is fatigue ($T = 58$).

Summary:

These preliminary results from our first 24 subjects suggest that current mood state has changed over time in PGW veterans on test-retest measures over a four-year interval. Specifically, mood complaints have become slightly less robust. These results will be discussed as they relate to follow-up neuropsychological test performance and social and occupational functioning in this group of PGW-deployed veterans.